



The role of autoimmune testing in chronic idiopathic urticaria

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ABSTRACT

Background: The clinical implications of autoimmune testing in chronic idiopathic urticaria (CIU) are not well established.

Objective: To identify the association of autoimmune biomarkers in CIU with disease severity.

Methods: We retrospectively evaluated 195 patients with a diagnosis of CIU for the presence of antinuclear antibody (ANA), anti-thyroglobulin antibody (ATG), anti-thyroperoxidase antibody (ATPO), and Chronic Urticaria (CU) Index. The patients were categorized into controlled and refractory subgroups based on their response to antihistamines with or without a leukotriene receptor antagonist.

Results: The percentage of patients with a positive test for ANA (titer > 1:160), ATG, ATPO, and CU Index were 29%, 6%, 26%, and 38%, respectively. Among those tested, the percentage of patients categorized as refractory was significantly higher in those with a positive CU index (80% vs 46%; $P = .01$) or a positive ANA titer (50% vs 30%; $P = .04$) than those with negative test results; however, a similar relationship was not observed for ATPO or ATG antibodies. Odds ratios of individual or combinations of autoimmune biomarkers in CIU were examined for associations with refractoriness to antihistamines with or without a leukotriene receptor antagonist. The CU Index alone has an odds ratio of 4.5 ($P = .005$), whereas the combination of ANA, ATG, and ATPO has an odds ratio of 3.1 ($P = .01$) and ANA alone has an odds ratio of 2.3 ($P = .04$) for correlating with a refractory outcome.

Conclusion: Our data indicate the CU Index independently has the strongest correlation with disease severity followed by the combination of ANA, ATG, and ATPO and the ANA alone.

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Introduction

Chronic Idiopathic Urticaria (CIU) is defined as the presence of hives, either continuously or intermittently, for 6 weeks without any identifiable cause. It has an estimated prevalence of 0.5 to 5% and impacts 15 to 25% of the population at some point in their lives.^{1,2} It is thought to have the most impact on quality of life of any allergic disease and to be similar in severity to triple-vessel coronary artery disease.^{1,3} Current guidelines recommend a stepwise approach using non-sedating H1 antihistamines up to 4× dosing as an initial therapy supplemented by H2 antagonists and leukotriene modifiers. These medications are generally well tolerated and used by most CIU patients to achieve control. However, a subset of patients have a more severe disease course and remain refractory to these conventional medications; such patients require stronger medications, including immunomodulators (eg, cyclosporine, tacrolimus, or mycophenolate), systemic corticosteroids, and possibly omalizumab to achieve control.^{4–9} Ascertaining which patients

will remain “controlled” or “refractory” on conventional therapy is challenging at the outset. To this end, many studies have attempted to look at laboratory parameters, particularly autoimmune markers, as surrogate indices of severity that may help predict disease course.^{1,10,11} Such categorizations could prove useful in allowing clinicians to “differentially” manage patients rather than employing a standard “stepwise” approach.

Over the past 2 decades, studies have suggested an autoimmune mechanism underlying the pathophysiology of CIU in up to 50% of the patients.¹² Auto-antibodies to the alpha chain of the high-affinity immunoglobulin E (IgE) receptor (FcεR1α) have been most commonly implicated in its pathogenesis.^{12,13} Historically, clinicians have also observed an association between CIU and thyroid antibodies in approximately 15 to 25% of CIU patients.^{1,14,15} Although the pathophysiology behind this association remains unclear, some consensus has been reached among allergists that it likely represents an epiphenomenon and that the benefit of thyroid supplementation for patients without overt hypothyroidism is unclear.^{16,17} Many clinicians have used the autologous serum skin test or other markers such as antinuclear antibodies (ANA) or antithyroid antibodies (ATA) to screen for evidence of autoimmunity in CIU. In the past 4 to 5 years, however, multiple commercial basophil histamine release assays have been developed and made available

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Table 1
Patient characteristics and tests performed

	N (%)
Total CIU patients	195
Male: female	52 (27%):143 (73%)
Age	42.6 (19–88) (Male = 46.1; Female = 41.3)
Concurrent angioedema	21 (11%)
CU index	81 (41%)
ANA	131 (67%)
ATG	118 (61%)
ATPO	112 (57%)

to screen for a functional autoantibody to FcεR1α.^{18,19} One such assay is the Chronic Urticaria (CU) Index (IBT-Viracor Labs, Lenexa, Kansas). The CU Index has primarily served as a qualitative measure of autoimmunity in CIU patients. However, we recently published data suggesting that this particular assay not only has qualitative value but also appears to have quantitative significance in its association with disease severity in CIU patients and is frequently elevated in refractory patients.¹¹ Given the characteristics of the CU Index, we hypothesized that a more comprehensive screening of autoimmune biomarkers would enhance our ability to predict disease severity in CIU. The purpose of this retrospective study was to determine whether screening of other biomarkers for autoimmunity, such as ANA or ATA, either individually or in combination with the CU Index, would better correlate with disease severity in our CIU cohort and to generate testable hypotheses for future prospective trials.

Methods

Patient population and design

This study was an institutional review board–approved retrospective analysis of adult patients with an ICD-9 diagnosis of chronic idiopathic urticaria from October 1, 2007 through September 30, 2009 seen in the allergy clinic at a tertiary-care academic referral center. Two hundred seventy patients (age > 18) were initially screened. These patients were further independently evaluated (by R.K.V. and M.J.B.) to confirm a diagnosis of CIU (presence of intermittent or continuous hives for > 6 weeks without an identifiable cause), resulting in 195 patients used for our analysis. Patients were excluded if they had primarily physical or cholinergic urticaria, acute urticaria, food or drug-related urticaria, vasculitis, mastocytosis, or exclusively angioedema without evidence of urticaria. Patients were categorically classified into 2 groups: they were considered *controlled* if they required only H1/H2 antihistamines with or without a leukotriene receptor antagonist (LTRA) for control of their hives or *refractory* if they continued to have physical evidence of urticaria (even if they reported subjective control) on this regimen. The control status of 5 (3%) patients could not be determined because of a loss to follow-up. Demographic data including age, sex, race, and concurrent diagnoses were obtained. Detailed analysis of urticaria medication usage was also evaluated. Laboratory data collected included ANA, anti-thyroperoxidase antibody (ATPO), anti-thyroglobulin antibody (ATG), and CU Index (IBT-Viracor Labs). For all tests, reference laboratory guidelines for a positive result were used including the CU Index (>10) and ANA (titer > 1:160).

Statistical analyses

Comparative analysis of autoimmune profiles among controlled and refractory subgroups was performed using the 2-tailed Fisher exact test, and $P < .05$ was considered significant. Contingency table (2 × 2) analyses were performed to determine test characteristics (sensitivity, specificity, positive predictive

value, and negative predictive value) and odds ratios for various laboratory test combinations for associations with disease course in CIU. Not all patients had every autoimmune biomarker measured, and therefore analyses were performed using the respective subsets of patients.

Results

Patient demographics

Data regarding patient characteristics and testing profile performed are shown in Table 1. All four biomarkers (CU Index, ANA, ATG, ATPO) were measured in 25% of CIU patients, and at least 1 biomarker was measured in 84% of patients. No autoimmune biomarker was measured in 32 (16%) CIU patients. The timing of the autoimmune biomarker assessments relative to onset of CIU could not be captured reliably. A more detailed description of patterns of laboratory tests checked in the cohort is shown in eTable 1.

Percentage of patients with positive autoimmune biomarkers

The percentage of patients with each positive autoimmune marker is shown in Figure 1. Among females, positive results for ANA, ATG, and ATPO were higher at 34%, 8%, and 30%, respectively. Among all patients with positive ANA results, a titer of 1:160 was noted in 14 patients, 1:320 in 12 patients, a titer greater than 1:320 in 11 patients, and nonnumerical positive in 1 patient.

Autoimmune biomarkers and disease severity

For an assessment of disease severity, CIU patients were categorized into 2 groups: controlled or refractory to antihistamines with or without the use of an LTRA. Of the 195 patients, 122 (63%) were controlled, 68 (35%) were refractory, and 5 (3%) were undetermined. As shown in Figure 2, in patients with positive CU Indices, the percentage of patients categorized as refractory was 80%, compared with 46% for those with negative CU Indices ($P = .01$). Similarly, in patients with positive ANA titers, the percentage of refractory patients is 50% compared with 30% in those with negative ANA titers ($P = .04$). In contrast, for ATG and ATPO, the percentage of refractory patients did not differ significantly between those with positive or negative test results.

Test characteristics of combinations of autoimmune biomarkers

Using the same categorical definition of controlled and refractory status of patients, we examined the test characteristics of individual and combinations of various autoimmune biomarkers and their association with disease severity. When multiple biomarkers were examined, a given combination was considered positive if any of the tests were positive. As shown in Figure 3, using a contingency table analysis for odds ratios, a positive CU Index was

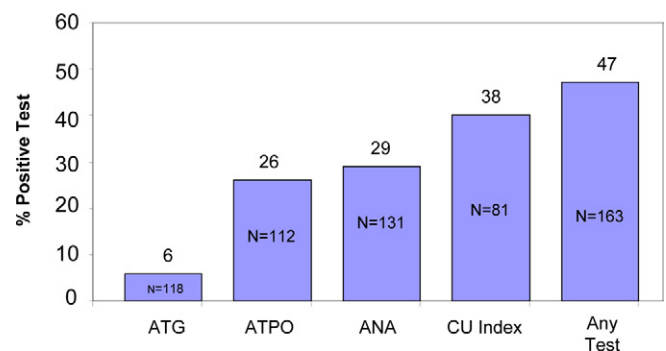


Fig. 1. Percentage of patients with positive autoimmune biomarkers in our CIU cohort. Values for each autoimmune marker and all of them combined are shown. The values are based on the subset of patients (N values shown) in whom the respective tests were performed.

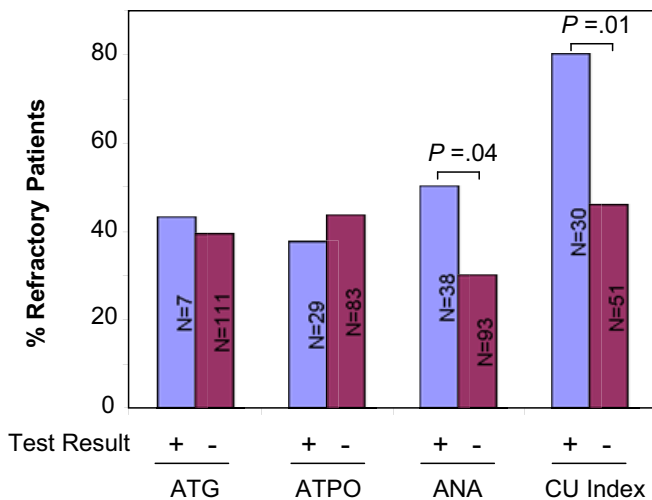


Fig. 2. Percentage of patients that are refractory for each test result. For each test, the percentage of patients that are refractory with indicated positive (+) or negative (–) test result are shown (N values shown). Statistically significant differences are shown with their corresponding *P*-value.

noted to have an odds ratio of 4.5 ($P = .005$) for identifying patients with CIU that were refractory to the use of antihistamines with or without LTRA. A positive ANA has an odds ratio of 2.3 ($P = .04$) for identifying a similar outcome. However, the combination of the CU Index and ANA testing as well as ATG and ATPO individually or in combination with the CU Index did not improve the ability to identify refractory patients. Interestingly, the combination of ANA with ATG and ATPO had an odds ratio of 3.1 ($P = .01$) for identifying a refractory patient. A more complete examination of combinations of autoimmune biomarker testing performed, and their respective odds ratios are shown in Table 2.

We also examined test characteristics such as sensitivity (SENS), specificity (SPEC), positive predictive value (PPV), and negative predictive value (NPV) for individual autoimmune biomarkers and many autoimmune biomarker combinations. In Table 2, the CU Index has superior SPEC and PPV for identifying a refractory outcome in CIU, but combinations of ANA and anti-thyroid antibodies have slightly better SENS and NPV.

Discussion

Our retrospective analysis of a cohort of CIU patients revealed proportions of patients with positive autoimmune biomarkers consistent with previous reports in the literature. To assess disease severity, we chose to categorize patients as either controlled or refractory to the use of antihistamines with or without an LTRA.

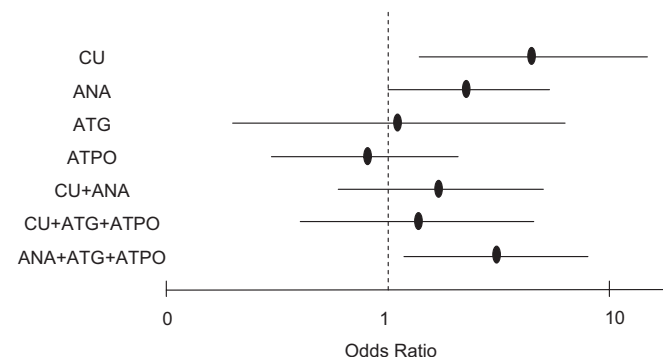


Fig. 3. Odds ratios for refractory patients. For the indicated tests and combination of tests, the oval represents the odds ratio and bar spans the 95% confidence interval on a log scale. The dashed line indicates an odds ratio of 1.

Table 2
Contingency table statistical analysis

	Odds Ratio (95% CI)	P value	SENS	SPEC	PPV	NPV
CU Index	4.5 (1.4–14.8)	.005	51%	82%	80%	54%
ANA	2.3 (1.0–5.4)	.044	40%	77%	50%	70%
ATG	1.1 (0.2–6.4)	NS	6%	94%	43%	60%
ATPO	0.8 (0.3–2.1)	NS	23%	72%	38%	57%
CU, ANA	1.7 (0.6–5.0)	NS	58%	55%	55%	58%
CU, ATG	1.9 (0.6–6.0)	NS	48%	67%	60%	56%
CU, ATPO	1.4 (0.4–4.6)	NS	53%	54%	59%	48%
ATG, ATPO	0.9 (0.4–2.3)	NS	26%	73%	40%	58%
ANA, ATPO	2.7 (1.1–6.7)	.024	57%	67%	57%	67%
ANA, ATG	3.1 (1.2–7.8)	.011	48%	77%	59%	68%
ANA, ATG, ATPO	3.1 (1.2–8.0)	.012	61%	67%	58%	69%
CU, ANA, ATG	1.4 (0.4–4.8)	NS	57%	52%	55%	54%
CU, ANA, ATPO	1.6 (0.4–6.1)	NS	64%	48%	62%	50%
CU, ATG, ATPO	1.4 (0.4–4.6)	NS	53%	54%	59%	48%
CU, ANA, ATG, ATPO	0.7 (0.2–2.6)	NS	55%	37%	41%	50%

Given the retrospective nature of our study, this straightforward classification of disease severity as a categorical variable could be confidently assessed and consistently applied to the review of all patient medical records. We demonstrate the utility of obtaining autoimmune biomarkers in CIU given the significant associations noted with disease severity. Furthermore, we show that the CU Index appears to have the best test characteristics, but is closely followed by the combination of ANA, ATG and ATPO, and the ANA alone for correlation with a refractory outcome in CIU.

Limitations of the study include its retrospective design and lack of standard protocol for assessment or management of CIU. As a result, only subsets of the cohort had any given pattern of autoimmune biomarker testing performed. Additionally, at the time of inclusion, patients were at most utilizing 2× daily antihistamine doses rather than the 4× dosing that is currently recommended²⁰; therefore, some of the patients defined as refractory may have been controlled if the higher antihistamine doses were used. Because this was a retrospective study, the determination of control was based on a subjective evaluation of the medical record (by R.K.V. and M.J.B.) rather than a validated instrument for disease activity such as the urticaria activity score.²¹ Also, our CIU cohort may represent a more severe subgroup of CIU given that our clinic is part of an academic referral center.

Based on previously published studies, the prevalence of auto-antibodies has been estimated to be approximately 30 to 50%.^{1,12} We observed that 47% of our patients had a positive value for any autoimmune biomarker, which concurs with these estimates. Using the CU Index, 38% of patients in our CIU cohort had positive values, which is consistent with previously published estimates for the functional FcεR1 antibody.²² We are unable to reliably comment on the prevalence of false-positive results for the CU index in the general population because insufficient data are currently available. However, a small study by Eckman et al²³ did report the prevalence of positive CU indices in both CIU patients (57%; $n = 21$) and healthy controls (23%; $n = 22$). Furthermore, our data show a presence of positive anti-thyroid antibodies at 6% for ATG and 26% for ATPO, also consistent with prior published estimates in CIU.^{1,14} In the general population, anti-thyroid antibodies (ATPO and ATG) have an estimated prevalence of between 3% and 14%.^{14,24} With regard to ANA, we report positive test results in 29% of patients in our CIU cohort. Although measuring an ANA could serve as a non-specific marker of autoimmunity, particularly in many rheumatologic disorders, its association with CIU is poorly understood and much less reported. A recent study reported a prevalence of 4% for

ANA among CIU patients.²⁵ Interestingly, ANA also appears to have a prevalence of between 5% and 20% (false positives) among healthy individuals without any underlying rheumatologic or autoimmune conditions.^{26,27} Our data might incorporate this nonspecific “false-positive” occurrence without any autoimmune mechanistic connection to CIU.

Recognizing the presence of these autoimmune biomarkers might be important to understanding the mechanism of CIU; however, another critical question is whether these autoimmune biomarkers have any clinical relevance or association with respect to disease severity or management. An analysis by Najib et al¹ found no correlation between a basophil activation test (BAT CD203) and the maximum number of medications used, which was their measure of disease severity. However, Sabroe et al¹⁰ demonstrated a correlation between clinical severity and presence or absence of serum histamine-releasing factors (which included autoantibodies to FcεR1, FcεRII, or IgE). In a recent study by Lapolla et al,²⁸ the authors found that a positive autoimmune finding (CU Index or BAT CD203) did not correlate with clinical severity. The analysis was performed on a small cohort of 20 patients, and disease severity was measured using mean total distinct medications used, which may not be an accurate reflection of severity. In another recent study, Tarbox et al²⁹ evaluated the utility of routine laboratory testing in CIU and concluded that such testing rarely leads to changes in management or better overall outcomes. Although this study was well powered with 356 patients, most of the patients had very mild disease, as only 61 patients (17%) were taking medications other than antihistamines with or without LTRA. No indication was reported of whether the patients were controlled on their existing medication regimen. Also, none of the patients had specific basophil histamine release assays or ASST performed, so the authors were unable to comment on the utility of such testing in CIU diagnosis and management. Furthermore, no attempt was made to find associations between laboratory findings and disease severity; rather, the outcome measure was whether a change in management was instituted. The possibility remains that an association between some of their laboratory findings (such as the ANA) and disease severity does exist, because this was not reported.

We demonstrated that the median CU Index value and the percentage of patients categorized as refractory were significantly higher in those with positive CU Indices compared with those with negative CU Indices (80% vs 46%; $P = .01$). We found a similar, though less robust, relationship for ANA in that the percentage of patients categorized as refractory was significantly higher in those with positive ANA titers than those with negative titers (50% vs 30%; $P = .04$). These results suggest that, although a positive ANA result does have some correlation with disease severity in CIU, a positive CU Index is more strongly associated with refractoriness to the use of antihistamines with or without LTRA. We were unable to find similar relationships for ATG or ATPO, which supports the possibility that their association with CIU may be an epiphenomenon without any clinical implications for disease severity.^{16,17}

To further address the clinical significance of these autoimmune biomarkers, we performed a rigorous comparative analysis of odds ratios and test characteristics (SENS, SPEC, PPV, NPV) on individual and combinations of biomarkers with respect to the patients' disease severity status, using our categorical definition. The CU Index independently has superior odds ratio, SPEC, and PPV in terms of an association with a refractory outcome in CIU. Using a contingency table analysis, patients with positive CU indices were nearly 5 times (OR 4.5) more likely to be refractory to antihistamines with or without LTRA than those with negative CU Indices. Likewise, the ANA and combinations of ANA with ATG and ATPO also have significant odds ratios to identify refractory patients (OR 2.3–3.1). The combinations of ANA with ATG and ATPO have slightly greater SENS and NPV compared with the CU Index alone, which indicates

that when the ANA or its combinations are negative, a greater likelihood exists that patients remained controlled on antihistamines with or without LTRA.

A great deal of interest has arisen in the use of omalizumab for the treatment of CIU based on recent clinical studies showing efficacy.^{8,9,30} However, omalizumab is an expensive medication, and it would be impractical to use as first-line therapy. Therefore, the ability to predict which patients are likely to be refractory to antihistamines would provide a valuable screening tool for patients that may require the use of omalizumab or immunomodulators and allow us to differentially manage patients and facilitate their more rapid use in the CIU population.

Another consideration in patient care is the cost of ordering the autoimmune biomarkers, for example, at our institution: the ANA, ATG, ATPO, and CU Index are \$84.20, \$128.00, \$118.00, and \$436.00, respectively. Of the various patterns of autoimmune biomarker testing in our cohort, the CU Index independently (\$436) had the strongest association with disease severity in CIU. The next best testing profile is the combination of the ANA, ATG, and ATPO, which would cost \$330.20, followed by the ANA alone, which would cost \$84.20. Given its superior test characteristics and higher cost, the overall cost-effectiveness of the CU Index for identifying refractory patients in CIU is unclear and will need to be further evaluated. A recent study estimated the annual direct and indirect health care costs in CIU to be approximately \$1,725 and \$322, respectively, with most of the costs being attributed to medications.³¹ The study also points out that the costs are substantially higher for patients with severe disease compared with mild disease. These findings further serve to highlight the need for establishing screening tools to help identify patients who are likely to remain refractory to conventional therapy and allow for an optimal and appropriate management in a timely and cost-effective manner.

To further validate our findings, we propose a prospective study of CIU patients assessed and treated using a standardized protocol. Central features of any future protocol would be (1) an assessment of all autoimmune biomarkers at an initial visit; (2) an evaluation of disease severity using a validated instrument such as the UAS7²¹; (3) an assessment of clinical response to classes of medications as refractory or controlled, and (4) management according to a current guidelines-based algorithm.⁴

Our results demonstrate that the presence of positive autoimmune biomarkers in CIU may have implications for disease severity and management. Of the various patterns of autoimmune biomarker testing in our cohort, the CU Index independently had the strongest association with disease severity in CIU followed by the combination of ANA, ATG and ATPO, and the ANA alone. These intriguing findings from our retrospective analysis are meant to generate “testable hypotheses” for future prospective studies incorporating additional measures of disease severity and standardized assessment and treatment algorithms to confirm these findings.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.anai.2012.02.018.

eTable 1
Numbers of patients with particular patterns of testing performed

	N (%)
CU, ANA	64 (33%)
CU, ATG	61 (31%)
CU, ATPO	54 (28%)
ATG, ATPO	113 (58%)
ANA, ATPO	96 (49%)
ANA, ATG	103 (53%)
ANA, ATG, ATPO	95 (49%)
CU, ANA, ATG	55 (28%)
CU, ANA, ATPO	49 (25%)
CU, ATG, ATPO	54 (28%)
CU, ANA, ATG, ATPO	49 (25%)